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Signed P. Mahoney

Dated 13 April 1999

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference SC/GM/N6797

2. Patent application number *(The Patent Office will fill th*
9805913.2
19 MAR 1998

3. Full name , address and postcode of the or of each applicant *(underline all surnames)*

KINGS COLLEGE UNIVERSITY OF LONDON
The Strand
London
WC2R 2LS

Patents ADP number *(if you know it)* 06669330001

If the applicant is a corporate body, give the country/state of its incorporation UNITED KINGDOM

4. Title of the invention
DIAGNOSIS OF MS

5. Name of your agent *(if you have one)* Williams, Powell & Associates

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
4 St. Paul's Churchyard
London
EC4M 8AY

Patents ADP number *(if you know it)* 5830310001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority appliation number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earleir UK application, give the number and the filing date of the earlier application.

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))
yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	5
Claim(s)	8
Abstract	
Drawing(s)	1 + 1

10. If you are filing one of the following, state how many against each item.

Priority documents	
translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/we quest the grant of a patent on the basis of this application.

Signature [signature] Date 19/03/98

12. Name and daytime telephone number of person to contact in the United Kingdom Mr Lee Anderson 0171 329 4400

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you form applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

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b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a sepate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

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Diagnosis of MS

This invention relates to the diagnosis of multiple sclerosis and other de-myelating diseases in humans.

In our copending application WO/9702667 we have disclosed a new diagnostic test for spongiform encephalopathy and other de-myelating conditions in mammals. The test disclosed in our prior application is based on a model of the genesis of this pathological state which is applicable to the various forms in which it is manifest in humans and other animals. In relation to the bovine spongiform disease this model provides an alternative to the current theory based on the formation of prions.

Briefly, this new model is based on the phenomenon of molecular mimicry according to which mammals exposed to certain bacteria having peptide sequences which mimic myelin peptides experience an auto-immune reaction. In our prior application we indicated that human myelinating diseases were also open to the same explanation according to our new model disclosed therein.

We have now confirmed the presence of elevated levels of certain antibodies in human sera of patients suffering from multiple sclerosis. These are the IgA antibodies to Acinetobacter species e.g. *Acinetobacter calcoaceticus*, the same organisms as were previously found in BSE sera.

Similar results have been obtained for Creuzfeldt-Jakob disease (CJD). Tests for the general class of Ig antibodies

in sera from patients who had died of CJD also show increased levels, this being especially marked for the IgA antibody sub-class. The same IgA specificity also applies to bovine sera used for the tests described in our above-mentioned copending application.

It is clear that humans suffering from MS and CJD and Cows suffering from BSE all have very significantly raised levels of *Acinetobacter calcoaceticus IgA antibodies* in their blood.

It is therefore possible for the first time by testing sera from living subjects at an early stage to identify those liable to develop MS and CJD.

This discovery opens up the possibility of early treatment of these infections e.g. by use of an appropriate antibiotic to prevent further auto-immune attack on the subjects' own myelin.

In view of the greater specificity of the IgA antibodies in the immune response it may be concluded that the mechanism of infection with *Acinetobacter* is via the mucous membranes of the body, the primary sites being the gut or the nasal passages. Since a further correlation has been observed between MS sufferers and patients with major sinus infections, it is probable that the nasal passages are the site of infection, resulting from inhalation of dust formed from dried sewage or animal excrement and carrying *Acinetobacter*. The knowledge of this mechanism implies the need for improved hygiene practices.

Experimental

The assay for the above mentioned organisms is described in our co-pending application the contents of which are hereby incorporated by reference. The method used is as follows:-

ELISA TEST

1) Aliquots of 200 ul of the diluted suspension of Acinetobacter grown in nutrient broth are absorbed onto 96 well flat bottomed rigid polystyrene microtitre plates overnight at 4°C.

2) The plates are then washed 3 times with phosphate buffered saline (PBS), 0.1% (v/v) Tween 20.

3) Aliquots of 200 µl of blocking solution (0.2% w/v ovalbumin, 0.1% v/v Tween 200 in PBS is added to each well and incubated for one hour at 37°C.

4) The plates are then washed 3 times with PBS.Tween 20.

5) Aliquots of 200 ul serum samples (test or control) diluted 1/200 in PBS.Tween 20 is added and incubated for 2 hours at 37°C.

6. The plates are then washed 3 times with PBS.Tween 20.

7) Aliquots of 200 ul of peroxidase conjugated rabbit anti-cow total immunoglobulin (or rabbit anti-human IgA or rabbit

anti-human IgG or rabbit anti-cow Iga or rabbit anti-cow IgG), diluted 1/4000 (cow) (or 1/500 for human) with PBS.Tween 20 are added and incubated for 2 hours at 37°C.

8) The plates are then washed 3 times with PBS.Tween 20.

9) The development of the colorimetric assay takes place at room temperature for 20 minutes, after the addition of 200 ul per well of 0.5 mg/ml (2,2'-azinobis(3-ethylbenz-thiazoline-6-sulphonic acid) in citrate/phosphate buffer, pH 4.1, containing 0.98 mM hydrogen peroxide.

10) the reaction is then stopped with 100 ul of 2 mg/ml sodium fluoride and optical densities measured at a wavelength of 630 nm with a micro-ELISA plate reader.

Results for MS and CJD are shown in the attached Figure...

From the foregoing it will be appreciated that the present invention comprises:

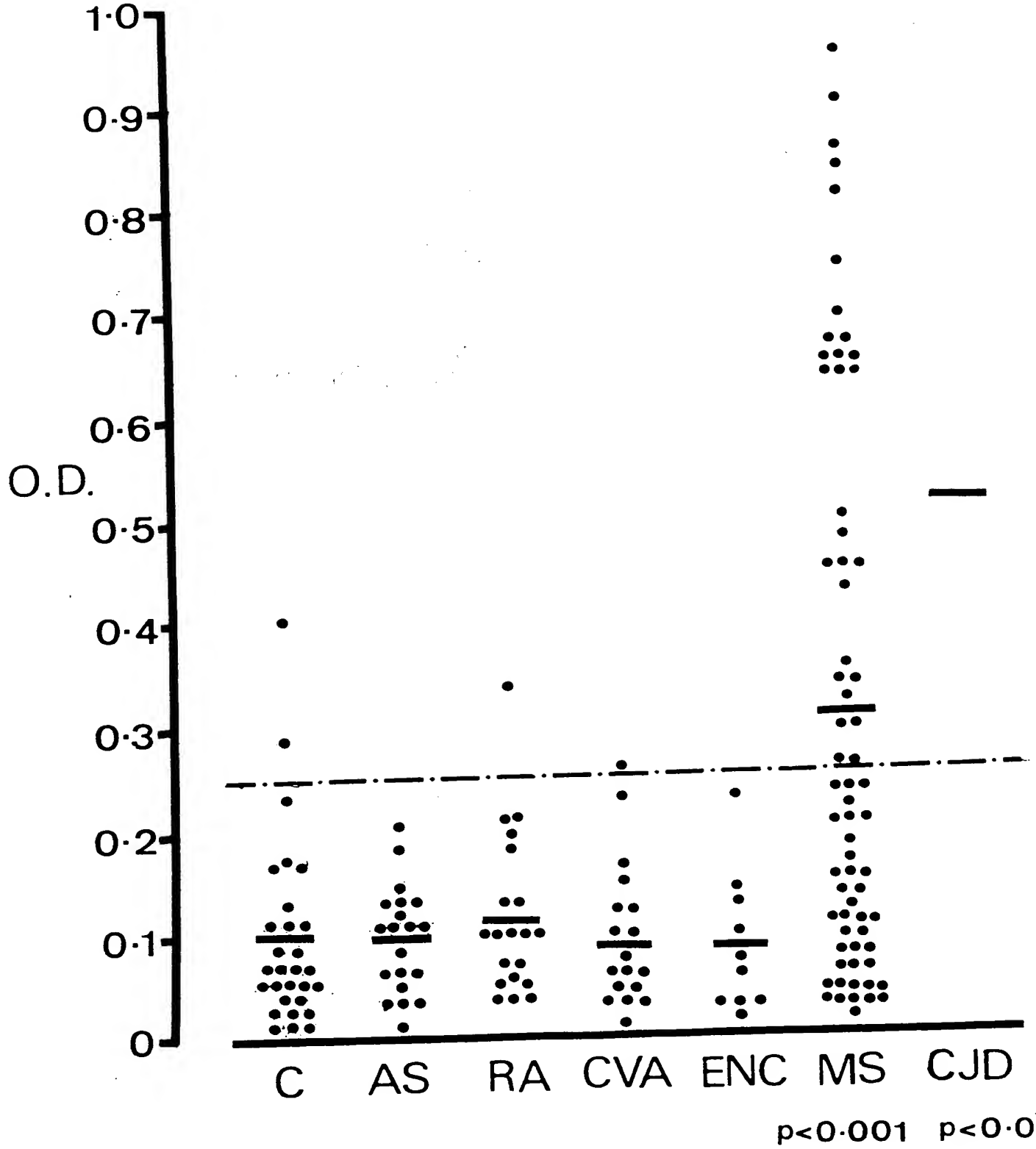
A method for early detection of MS or CJD in humans which comprises assaying a biological sample for antibodies to Acinetobacter calcoaceticus or a peptide derived therefrom.

A method as defined above in which the assay is for IgA antibodies.

A method as defined above in which a positive result is indicated by levels of antibodies at least about two standard deviations above that of control samples.

A method for early detection of BSE in cattle in accordance with our application WO/9702667 in which IgA antibodies are measured.

IgA Acinetobacter



Legend: IgA antibodies to Acinetobacter bacteria, measured by ELISA in healthy controls (C) and patients with ankylosing spondylitis (AS), rheumatoid arthritis (RA) cerebro-vascular accidents (CVA), viral encephalitis (ENC), multiple sclerosis (MS) and Creutzfeldt-Jakob disease (CJD). (p-values indicate significance compared to contr

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19-3-99

Williams Powell & Associates